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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/900,057	07/06/2001	Fayad Z. Sheabar	4532660/29930	7817

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EXAMINER

PATTEN, PATRICIA A

ART UNIT	PAPER NUMBER
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1654

DATE MAILED: 05/06/2003

4

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/900,057

Applicant(s)

Sheabar et al.

Examiner

Patricia Patten

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☐ Responsive to communication(s) filed on _____
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-16 is/are pending in the application.
- 4a) Of the above, claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-16 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
a) ☐ All b) ☐ Some* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
*See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).
a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892) 4) ☐ Interview Summary (PTO-413) Paper No(s). _____
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948) 5) ☐ Notice of Informal Patent Application (PTO-152)
- 3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____ 6) ☐ Other:

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DETAILED ACTION

Claims 1-16 are pending in the application. An examination of these claims follows.

Claim Objections

Claims 6, 8 and 9 are objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. In the Instant case, claim 6 recites an inherent property of the method and does not recite a particular method step. Thus, claim 6 does not further limit claim 4. For example, a definite method step would recite; 'The method of claim 4 wherein the heating step is conducted at a temperature greater than 75 °C'. Claims 8 and 9 also recite inherent properties of the method without actually limiting claim 1.

Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

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The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 4, 5, 12, 13 and 15 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 4 and 5 both recite 'filtrate'. This term lacks antecedent basis in claim 1 in that claim 1 did not specifically recite 'filtrate'.

Claim 12 states 'open, screen-channel membrane'. The Examiner cannot find a definition of this type of membrane in the Instant specification nor in the prior art. Is this a tangential membrane? It appears that the term may be repugnant to what is known as a 'tangential' membrane, but the Examiner is not sure. Ultrafiltration membranes are manufactured in various forms depending on the ultrafiltration apparatus. Because the Examiner cannot determine what an 'open-screen-channel membrane' is, the claims will be examined on the merits as if they were simply drawn to an ultrafiltration membrane.

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Claim 13 recites 'prior to filtration'. This phrase lacks antecedent basis in claim 1 because claim 1 did not specifically recite filtration.

Claim 15 recites 'the retentate'. This phrase lacks antecedent basis in claim 11 in that claim 15 did not specifically recite 'retentate'. Further, if claim 11 were amended to recite 'retentate' the claim would be confusing in that a retentate solution is typically formed via ultrafiltration and not simply filtration.

In order to overcome these rejections, it is suggested that Applicants either omit the phrases 'filtrate' and 'prior to filtration' respectively, or alternatively, amend claim 1 to recite a specific filtration step. It is further suggested that the ambiguity with regard to 'filtration' steps and the 'ultrafiltration' step be amended to clarify what specific protocol step is actually being applied in the claims.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless -

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(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-4 and 6-11 are rejected under 35 U.S.C. 102(b) as being anticipated by Ryan et al. (WO 99/01474).

Ryan et al. (WO 99/01474) taught a method for isolating proteinase inhibitor II from potato tubers via extraction with a solvent (water/ethanol/.88% formic acid and 1.5 M NaCl), filtration via cheesecloth, heating the liquid portion to 70 °C, cooling, evaporation of ethanol, centrifugation and ultrafiltration via dialysis with 12-14 Kd MW cutoff (p.9, Example 1 and claims 1-6).

Claim 6 recites '...wherein the purity of the protease inhibitor is increased by selecting a temperature greater than about 75 °C'. It is noted that this claim only recites an inherent property of the method and does not recite a particular method step. For example, a definite method step would recite; 'The method of claim 4 wherein the heating step is conducted at a temperature greater than 75 °C' (please also see Claim Objections *supra*).

Further, where claims 8 and 9 recite 'wherein as the temperature of the heat treatment step is increased, the duration of the heat treatment step is decreased' and

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'wherein as the temperature of the heat treatment step is decreased, the duration of the heat treatment step is increased' are inherent properties of the method. These claims do not recite specific method steps, and therefore do not further limit claim 1. It is deemed that with regard to claims 8 and 9, the same would be true for the method taught by Ryan et al.: i.e., if the temperature of the heat treatment was increased, the duration of the heat treatment is decreased, and if the temperature of the heat treatment is decreased, the duration of the heat treatment step is increased. It is further noted that this is a well known scientific principal, which does not limit the claims.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 1-11 and 13-16 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ryan et al. (WO 99/01474).

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The teachings of Ryan et al. were discussed *supra*. Ryan et al. did not specifically teach wherein the filtrate was heated for 30-180 minutes, wherein the protein was concentrated to 1/5 of the starting volume, wherein the clarified extract was added to ammonium bicarbonate prior to filtration, or wherein the filtration step further comprises washing with up to ten volumes of filtration buffer.

Please note that claim 13 was examined on the merits as if claim 1, part (d) recited filtration or ultrafiltration.

One of ordinary skill in the art would have been motivated to have concentrated the volume of the liquid protein slurry to 1/5 of the starting volume in order to de-salt the protein mixture in order to prepare the crude mixture for further purification such as column chromatography. The ordinary artisan would have recognized that the salt would need to be removed from solution in order to standardize the conductivity, thereby allowing the proteins to elute from the column based upon their respective ionic strengths.

One of ordinary skill in the art would have been motivated to heat the filtrate for 30-180 minutes in order to perform the method described by Ryan et al. It is clear from Ryan et al. That the temperature of the filtrate was raised to 70°C in a boiling water

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bath, and then transferred to a flash evaporator with a temperature of 50°C (i.e., Example 1). Therefore, it is deemed that raising the temperature of the liquid extract and then lowering the extract temperature to evaporate the ethanol were both sequential heating steps, because during evaporation, the extract continued to be heated. The ordinary artisan would have recognized that heating the extract to denature the proteins, and then evaporation of the ethanol for 30-180 minutes would have been a suitable time period in order to have completed the heating/evaporating process.

Although Ryan et al. did not specifically teach wherein the clarified extract was added to ammonium bicarbonate prior to filtration, they did teach that the precipitated proteins were advantageously dissolved in 0.1 M ammonium bicarbonate (p.8, lines 25-26). Ryan et al. mentioned that the addition of ammonium bicarbonate was 'suitable for solubilization and subsequent lyophilization - *a known method for stable storage of protease inhibitors*' (p.8, lines 25-27, emphasis added). Therefore, one of ordinary skill in the art would have been motivated to have added ammonium bicarbonate buffer prior to filtration in order to stabilize the protein thereby effecting a greater overall yield.

One of ordinary skill in the art would have been motivated to have washed the final protein product to remove any unwanted contaminants. Washing proteins with

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storage buffer was old and well known in the art of protein purification, as well as other forms of purification. The ordinary artisan would have had a reasonable expectation that washing the final protein precipitate would have 'cleaned-up' the protease, thereby creating a protease with greater activity as well as better stability upon storage.

Claim 12 is rejected under 35 U.S.C. 103(a) as being unpatentable over Ryan et al. (WO 99/01474) as applied to claims 1-11 and 13-16 above, and further in view of Borud (EP 0487480 A2).

The teachings of Ryan et al. were discussed *supra*. Ryan et al. did not specifically teach wherein filtration (ultrafiltration) was conducted on a membrane which had a MW cut-off of about 5 - 10 Kd (please note again that this claim was not examined on the merits for 'open-screen channeled membrane'). Ryan et al. did teach however that '...other methods of dialysis, solute exchange, or precipitation that may yield a better or more rapid recovery of the proteinase inhibitors can be substituted. The precipitated proteins may be recovered by filtration, centrifugation or other methods".

Borud (EP 0487480 A2) disclosed a method for purification of a proteinase inhibitor which comprised separation of potato solids from the water-soluble liquid via

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high speed grating and sieving or centrifuging (col.3, lines 7-33). A summary of small - scale production of the proteinase inhibitors was discussed on col.5, lines 33-49:

Hydrochloric acid (solvent) was added to the liquid potato extract to bring the pH to about 4.4 (col.5, lines 3-4 and lines 44-45). Proteins were coagulated by heating for 5-10 minutes at 65-70 °C followed by cooling to 20°C (col.5, lines 45-48).

The coagulated (precipitated) proteins were removed via filtration (col.5, lines 48-49), and the remaining liquid (clarified extract solution) was concentrated via ultrafiltration with a DDS-FILTRATION equipment which employed a polysulfone membrane with an average pore size of 10 Å , MW cut off of about 10 Kd ($10 \text{ Å} \approx 0.01 \text{ }\mu\text{m}$) (col.6, lines 25-29). The flux of the retentate was reported at 70 L permeate/m²/h (col.6, line 29) which approximately equals .11 L/ft²/min ($1 \text{ m}^2 = 10.76 \text{ ft}^2$).

One of ordinary skill in the art would have been motivated to ultrafiltrate the final protein product via a membrane having a MW cut off of about 10 Kd in order to have successfully purified a protease inhibitor from potato. It was clear from Borud that a membrane with a molecular weight cut-off with 10 kD (within the Instantly claimed range) would have allowed lower molecular weight molecules to traverse the membrane, while the protease inhibitors were forced back through into the retentate solution.

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From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

No Claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner Patricia Patten, whose telephone number is (703)308-1189. The examiner can normally be reached on M-F from 9am to 5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor Brenda Brumback is on 703-306-3220. The fax phone number for the organization where this application or proceeding is assigned is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.



CHRISTOPHER R. TATE
PRIMARY EXAMINER